FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
202306US0PCT	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
09/774181	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03838	02 JUNE 1999	NONE

TITLE OF INVENTION

USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

APPLICANT(S) FOR DO/EO/US

Bernhard A. SABEL, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/774181	PCT/EP99/03838	202306US0PCT

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1,000.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$860.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☒ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	21 - 20 =	1	x $18.00	$18.00	
Independent claims	2 - 3 =	0	x $80.00	$0.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,008.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☒	$504.00	
SUBTOTAL =				$504.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00	
TOTAL NATIONAL FEE =				$504.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00	
TOTAL FEES ENCLOSED =				$504.00	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$504.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Surinder Sachar
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Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

2-2-01
DATE

202306US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

BERNHARD A. SABEL ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLICATION:
(BASED ON PCT/EP99/03838)

FILED: HEREWITH :

FOR: USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please cancel Claims 1-10 and 12-14.

Please add the following claims:

--15. A method of treating cancer comprising;

administering a nanoparticle to a patient in need thereof; wherein said nanoparticle comprises polymeric material, one or more substances physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizers which allow

targeting of said physiologically effective substances to a specific site within said mammalian body, and/or a surfactant coating on said nanoparticles.

16. The method of Claim 15, wherein said nanoparticle formulated in a composition which further comprises a physiologically acceptable carrier and/or diluent.

17. The method of Claim 15, wherein said cancer is brain cancer.

18. The method of Claim 15, wherein said polymeric material has a diameter of below 1,000nm.

19. The method of Claim 18, wherein said polymeric material has a diameter of from 1 to 1,000 nm.

20. The method of Claim 15, wherein said polymeric material is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyacrylamides, polylacetates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes; derivatives; copolymers and mixtures thereof.

21. The method of Claim 15, wherein said physiologically effective substances are adsorbed, absorbed and/or incorporated in the nanoparticles.

22. The method of Claim 15, wherein said physiologically effective substances comprises one or more chemotherapeutic agents for the cancer treatment.

23. The method of Claim 22, wherein said chemotherapeutic agents are selected from the group consisting of alkylating agents, antimetabolites, natural anticancer products, hormones, metal co-ordination complexes and mixtures thereof.

24. The method of Claim 22, wherein said chemotherapeutic agents are selected from the group consisting of nitrogen mustards, nitroso ureas, ethylene imines, methylmelamines,

folic acid analogs, pyrimidine analogs, purine analogs, vinca alkaloids, epipodophyllotoxins, antibiotics, estrogens, gonadotropin-releasing hormon analogs, antiestrogens, androgens, platinum complexes and mixtures thereof.

25. The method of Claim 22, wherein said chemotherapeutic agents are doxorubicin and/or mitoxantrone.

26. The method of Claim 15, wherein the stabilizer and/or surfactant coating material is selected from the group consisting of stabilizers/surfactants which allow a passage of said nanoparticles including said physiologically effective substance(s) across the blood brain barrier in said mammal and stabilizers/surfactants which allow a release of said physiologically effective substance(s) from said nanoparticles and a passage of said substance(s) across the blood brain barrier separate from said nanoparticles.

27. The method of Claim 26, wherein said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbates, dextrans, carboxylic acid esters of multifunctional alcohols, polyoxamers, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated monoglycerides, alkoxylated diglycerides, alkoxylated triglycerides, alkoxylated phenols, alkoxylated diphenols, substances of the Genapol^{R} and Bauki^{R} series, metal salts of carboxylic acids, metal salts of alcohol sulfates, and metal salts of sulfosuccinates and mixtures of two or more of said substances.

28. The method of Claim 26, wherein said stabilizer/surfactant comprise a substance selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 81, polysorbate 85, dextran 12,000, dextran 70,000, fatty acid esters of glycerol and sorbitol as glycerol monostearate, sorbitan monostearate, sorbitan monooleate, polyoxamer 188 (Pluronic R F68), ethoxylated ethers, ethoxylated esters,

ethoxylated triglycerides, ethoxylated phenols and diphenols, metal salts of fatty acids, and metal salts of fatty alcohol sulfates.

29. The method of Claim 26, wherein said stabilizer/surfactant comprise a substance selected from the group consisting of sodium salts of fatty acids, sodium salts of fatty alcohol sulfates and mixtures of two or more of said substances

30. The method of Claim 26, wherein said stabilizer/surfactant comprise sodium stearate and/or sodium lauryl sulfate.

31. The method of Claim 26, wherein said stabilizer/surfactant comprise a substance selected from the group consisting of polysorbate 80, polysorbate 85, dextran 12,000, dextran 70,000 and mixtures thereof.

32. The method of Claim 16, wherein said carrier and/or diluent are selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts and/or buffers.

33. The method of Claim 15, wherein said administering is intravenous administering.

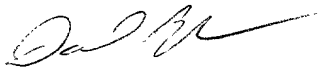
34. The method of Claim 15, wherein said mammal is a human.--

REMARKS

Claims 11 and 15-34 are active in the present application. Support for Claims 15-34 is found in Claims 1-14 and the specification as filed herewith. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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DOCKET NO: 202306US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :
Bernhard A. SABEL, et al.

SERIAL NO: NEW U.S. PCT APPLICATION :
(Based on PCT/EP99/03838)

FILED: HEREWITH :

FOR: USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

LETTER REGARDING CLAIM TO SMALL ENTITY STATUS

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Applicant(s) hereby give notice that Small Entity Status is claimed in the above-identified application.

Our check in the amount of $504.00 - is attached hereto. If any variance exists between the amount enclosed, please charge or credit the difference to our Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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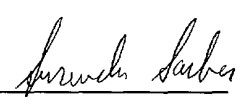

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Use of Drug-Loaded Nanoparticles for the Treatment of Cancers

The present invention relates to the use of drug-loaded nanoparticles for preparing a medicament for the treatment of cancer, particularly for the treatment of cancer in the brain, even more particularly for the treatment of brain cancer in humans. The invention also relates to a process for the treatment of brain cancer, particularly for the treatment of brain cancer in humans, by administering an effective amount of nanoparticles containing a substance which has effect in the cancer treatment or has immunosuppressive effects.

It was reported in the U. S. Patent Application S. N. 08/203,326 and the parallel International Patent Application No. PCT/EP 95/00724 (corresponding to WO 95/22963) that drugs may be delivered to the body of mammals, particularly to the body of humans, and may be transported across the blood brain barrier (furtheron referred to as "bbb") by means of nanoparticles to which drugs are complexed (incorporated, adsorbed or absorbed) and which are surrounded by a coating made of an appropriate surfactant. A similar teaching can be found in the pending International Patent Application No. PCT/EP 97/03099. It was taught in both of said applications that the drug may be an immunosuppressive or anticancer agent. As the appropriate surfactant, there were taught a number of generally and commercially available surfactants as, for example, Polysorbate ^{R} 80 or Tween ^{R} 80.

It is general knowledge that the non-invasive treatment of cancers in the brain of mammals, particularly in the brain of humans has to rely on very small amounts of immunosuppressive or anticancer medicaments or drugs which are transported to the desired target, i. e. the tumor in the brain. In particular, anticancer agents known to have a high effect in the anticancer treatment do not at all or do not in a sufficiently effective amount pass the blood brain barrier (bbb) and are effective only when delivered directly into the brain. Such a delivery step, however, means a delivery into the skull at a suitable point which is a very complicated and sometimes risky surgery step.

The term "blood brain barrier " (bbb) as used herein refers to the bbb in the narrower sense, i. e. in the sense this term is used usually by a person skilled in the medical field, as well as to the blood spinal barrier and blood retina barrier.

It was now surprisingly found that nanoparticles prepared in accordance with teachings of the prior art, particularly of the above two Patent Applications, may be loaded with a substance having effect in the treatment of cancers, particularly having effect in the treatment of cancers in the brain, for example in humans, in an effective amount and may then be coated with a suitable surfactant so as to allow that drug-loaded nanoparticles to pass across the bbb and to deliver the effective drug to the site where it may exhibit its anticancer and/or immunosuppressive activity. It was particularly found that, by a suitable selection of the combination drug/surfactant, an effective use of such nanoparticles loaded with the drug and coated with a surfactant in the treatment of cancers, particularly of cancers in the brain, may be proviced.

Hence, the invention relates to the use of nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within or on said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the manufacture of a medicament for the treatment of cancer in said mammal.

In a preferred embodiment of the present invention, the treatment of cancer is a treatment of cancer in the brain. In an even more preferred embodiment, the brain cancer treatment is a treatment to a human. The terms "cancer" and "tumor(s)" are used in the description and claims in a synonymous manner.

The nanoparticles used in the present invention for the cancer treatment are nanoparticles which mainly consist of three major components, i. e. the polymeric material which is used to form a wall either incorporating the drug or physiologically effective substance(s) or containing said substance(s) adsorbed or absorbed thereto, e. g. onto its surface; the physiologically effective substance or substances contained within or on said nanoparticle; and a stabilizer or more than one stabilizer allowing the passage of said nanoparticle across the bbb.

Although there are basically no limitations with respect to any of the above three components and their combinations, as long as they allow the achievement of the intended goal, the present invention comprises as one of the preferred embodiments the use of said nanoparticles, wherein said nanoparticles comprise particles of said polymeric material having a diameter of below 1,000 nm, preferably of from 1 to 1,000 nm.

In a further preferred embodiment, the invention relates to the use of said nanoparticles, wherein said polymeric material the nanoparticles are consisting of is selected from the group consisting of polyacrylates, polymethacrylates, poly-cyanoacrylates, polyacrylamides, polylactates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacroöein, polyglutaraldehydes and derivatives, copolymers and mixtures thereof. There is of course no limit with respect to the specific material of the nanoparticles, as long as the material used allows or even promotes the successful transport to and passage across the bbb of the physiologically effective substanc or substances.

In accordance with the present use of the nanoparticles according to the invention, there is/are provided within or on said nanoparticles (incorporated, absorbed and/or adsorbed) one or more substances which are physiologically effective in the treatment of cancer upon

delivery to a mammal. The substances may be a single substance or may be two or even more substances which may act on the human body on a separate route or on a combined route or even synergistic route.

In a preferred use according to the present invention, said physiologically effective substance(s) to be delivered to said mammal comprise(s) one or more chemotherapeutic agent(s) for the cancer treatment, particularly for the treatment of cancer in the brain of said mammal, more particularly for the treatment of cancer in the human body, i. e. the brain. Such delivery of anticancer agents to the human brain was very difficult in the prior art, what concerns the effective amounts which could be provided to the site of action of the chemotherapeutic agent; surprisingly, the use of the present invention provides an effective and controllable amount of such substance(s) at the site of their action in an easily administrable composition.

In accordance with the present invention, such a use of said nanoparticles is preferred, wherein said chemotherapeutic anticancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural anticancer products, hormones, metal co-ordination complexes and mixtures thereof. There is no restriction concerning the administration of substances of one single group or of more than one of the above groups which, of course, include numerous substances specifically mentioned above. There is only the requirement that these substances may be suitably incorporated into or adsorbed onto or absorbed by said nanoparticles used in the present invention and do not interfere with each other during such a use.

As specific substances for a use in accordance with a preferred embodiment of the invention, there may be mentioned the following substances, without restricting the inventive use to the substances mentioned below:

- nitrogen mustards, e. g. Cyclophosphamide, Trofosfamide, Ifosfamide and Chlorambucil;
- nitroso ureas, e. g. Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU) and Nimustine (ACNU);
- ethylene imines and methyl-melamines, e. g. Thiotepa;
- folic acid analogs, e. g. Methotrexate;
- pyrimidine analogs, e. g. 5-Fluorouracil and Cytarabine;
- purine analogs, e. g. Mercaptopurine and Azathioprine;
- vinca alkaloids, e. g. Vinblastine, Vincristine and Vindesine;
- epipodophyllotoxins, e. g. Etoposide and Teniposide;
- antibiotics, e. g. Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Bleomycin A2, Mitomycin C and Mitoxantrone;
- estrogens, e. g. Diethyl stilbestrol;
- gonadotropin-releasing hormon analogs, e. g. Leuprolide, Buserelin and Goserelin;
- antiestrogens, e. g. Tamoxifen and Aminoglutethimide;
- androgens, e. g. Testolactone and Drostanolonproprionate; and
- platinum complexes, e. g. Cisplatin and Carboplatin.

According to the invention, mixtures of the above substances may also be used as long as they result into a successful treatment of cancer, particularly of brain cancer, in mammals as for example in humans. Particularly preferred in the use of the nanoparticles of the püresent invention are Doxorubicin and/or Mitoxantrone, since the administration of any of these substances by using nanoparticles results into a successful anticancer treatment, particularly a successful treatment of brain tumors in mammals as for example in humans. In particular, a passage of the bbb by said substance in a therapeutically effective amount was observed, which fact was completely surprising for a skilled person being familiar with the prior art problem of providing a therapeutically effective amount of said anticancer agents in the brain.

A critical component of the nanoparticles used in the present invention is/are the stabilizer(s). In a preferred use, only one stabilizer is used whereby a passage of the bbb by said nanoparticles loaded with the anticancer drugs can be afforded in a successful way, and the anticancer drugs in said nanoparticles are directed to the tumor site in the brain in a high concentration. This was not yet possible in the prior art approaches. As a result thereof, the treatment of brain cancers could be considerably improved, and the success rates of the treatment could be increased as well.

The other critical component of the nanoparticles used in the present invention are the surfactant materials of the coating which materials are belonging to the same group of compounds as the above. The stabilizer may be present in the nanoparticles used in accordance with the present invention as a result of the manufacturing steps either in small remaining amounts or may form the coating allowing the passage of the effective substance(s) across the bbb. As an alternative, the separate coating may be provided. As a result, the outside wall of the nanoparticles used in the present invention is coated with the material allowing the passage of the bbb in a surprising manner. The application of the coating or the provision of the stabilizer in such nanoparticles is basically described in the above-mentioned International Patent Applications the disclosures of which are incorporated herein by reference.

In a preferred embodiment of the present inventive use, the material(s) of the stabilizer/ surfactant is/are selected selected from the group consisting of stabilizers/surfactants which allow a passage of said nanoparticles including said physiologically effective substance(s) across the blood brain barrier in said mammal and stabilizers/surfactants which allow a release of said physiologically effective substance(s) from said nanoparticles and a passage of said substance(s) across the blood brain barrier separate from said nanoparticles. It is furthermore preferred that said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbates, dextrans, carboxylic acid esters of multifunctional

alcohols, polyoxamers, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di- and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol [R] and Bauki [R] series, metal salts of carboxylic acids, metal salts of alcohol sulfates, and metal salts of sulfosuccinates and mixtures of two or more of said substances.

Specific examples of said stabilizers and/or surfactants which are used for the coating for the nanoparticles are mentioned below, without restricting the invention to the compounds or groups of compounds mentioned below. Preferably, said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 81, polysorbate 85, dextran 12.000, dextran 70,000, fatty acid esters of glycerol and sorbitol as glycerol monostearate, sorbitan monostearate and sorbitan monooleate, polyoxamer 188 (Pluronic R F68), ethoxylated ethers, ethoxylated esters, ethoxylated triglycerides, ethoxylated phenols and diphenols, metal salts of fatty acids and of fatty alcohol sulfates, more preferably the sodium salts of fatty acids and of fatty alcohol sulfates, even more preferably sodium stearate and sodium lauryl sulfate, and mixtures of two or more of said substances.

The most preferred stabilizers/surfactant materials are selected from the group consisting of polysorbate 80, polysorbate 85, dextran 12,000 or dextran 70,000 and mixtures thereof and mixtures of said stabilizers with other stabilizers. With the latter compounds, a superior use of the nanoparticles in the anticancer treatment can be achieved, particularly in the treatment of brain cancers in humans.

It is an accordance with a further preferred use of the nanoparticles, if said carrier and/or diluent which is used for the administration of the nanoparticles used in the present invention is/are selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts and/or buffers and any other solution acceptable for administration to a mammal.

In accordance with the invention, there are further provided nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the treatment of cancer in said mammal.

In another aspect of the invention, there is provided a process for the treatment of cancer, particularly of brain cancer, in mammals, said process comprising the step of administering to said mammals nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, in an amount effective for the treatment of cancer.

In a preferred process according to the invention, the administration is an i.v. administration. It is particularly preferred that the treatment is a treatment of brain cancer, e. g. in mammals as for example humans.

The invention is further exemplified by the subsequent example which, however, should not be understood to limit the invention.

The anti-tumor effect of doxorubicin preparations was tested in rats with an intracranially transplanted glioblastoma 101/8. This tumor is known to have a substantial number of receptors to the epidermal growth factor.

The animals were treated with 1.5 mg/kg x 3 of doxorubicin which makes a total course dose of 4.5 mg/kg (the total dose for mice is usually 7 to 8 mg/kg).

The drugs were administered i/v on the day 2 (48 h after implantation of the tumor), day 5 and day 8 after tumor implantation.

The experiment was started on 9 to 13 December 1998 and was not yet completed by 20 May 1999 since some of the animals are still alive.

Drug preparations were administered as usual in saline or in 1 % Tween ^{R} 80 . For the coating of the nanoparticles loaded with doxorubicin, the suspension was added with 1 % Tween ^{R} 80 with stirring. The mixture was incubated for 2 h.

It can be seen from the subsequent tables that in the case that doxorubicin was administered ("Dox"), the rats died after the times (hours, h) given in column 1 of the upper table. In the case of the administration of the drug with Tween 80, most of the rats died, too. As in the first case, all rats died after administration of Tween 80 coated nanoparticles and doxorubicin-loaded nanoparticles without coating (columns 3 and 4 of the upper table). Only in the case that doxorubicin-loaded nanoparticles were coated with Tween 80, 3 of 8 rats survived.

This result clearly shows that the surfactant-coated nanoparticles were suitable to promote the passage of an effective dose of the anticancer agent doxorubicin across the bbb for a successful anticancer treatment.

Survival rate (days) of glioblastoma 101/8 bearing rats after i/v administration of doxorubicin preparations

Control	Dox	Dox + Tween 80	NP + Tween 80	Dox-NP	Dox-NP + Tween 80
9	11	13	9	13	22
11	13	13	11	13	22
12	14	23	11	15	22
13	14	38	12	15	23
13	14	51	18	17	37
13	15	alive	19	38	alive
14	20			40	alive
17	21			50	alive
17	23				

Group	Median survival time (MST, days)	Prolongation of MST %	Survivals (by day 60)
Control	13,2		
Dox	16,1	22	0/9
Dox-NP	25,1	90	0/8
Dox + Tween	27,6	112	1/6
Dox-NP + Tween	25,1	91	3/8
NP + Tween	13,3	0	0/6

Claims

1. Use of nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the manufacture of a medicament for the treatment of cancer in said mammal.

2. The use according to claim 1 for the treatment of brain cancer in said mammal.

3. The use according to claim 1 or claim 2, wherein said nanoparticles comprise particles of said polymeric material having a diameter of below 1,000 nm, preferably of from 1 to 1,000 nm.

4. The use according to any of the claims 1 to 3, wherein said polymeric material is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyacrylamides, polylactates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacroöein, polyglutaraldehydes and derivatives, copolymers and mixtures thereof.

5. The use according to any of the claims 1 to 4, wherein said nanoparticles comprise said physiologically effective substance(s) to be delivered to said mammal in the form adsorbed, absorbed and/or incorporated thereto.

6. The use according to any of the claims 1 to 5, wherein said physiologically effective substance(s) to be delivered to said mammal comprise(s) one or more chemotherapeutic agent(s) for the cancer treatment, preferably alkylating agents, antimetabolites, natural anticancer products, hormones, metal co-ordination complexes and mixtures thereof, more preferably nitrogen mustards, nitroso ureas, ethylene imines and methyl-melamines, folic acid analogs, pyrimidine analogs, purine analogs, vinca alkaloids, epipodophyllotoxins, antibiotics, estrogens, gonadotropin-releasing hormon analogs, antiestrogens, androgens, platinum complexes and mixtures thereof, even more preferred doxorubicin and/or mitoxantrone.

7. The use according to any of the claims 1 to 6, wherein the stabilizer and/or surfactant coating material is selected from the group consisting of stabilizers/surfactants which allow a passage of said nanoparticles including said physiologically effective substance(s) across the blood brain barrier in said mammal and stabilizers/surfactants which allow a release of said physiologically effective substance(s) from said nanoparticles and a passage of said substance(s) across the blood brain barrier separate from said nanoparticles, preferably wherein said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbates, dextrans, carboxylic acid esters of multifunctional alcohols, polyoxamers, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di- and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol ^{R} and Bauki ^{R} series, metal salts of carboxylic acids, metal salts of alcohol sulfates, and metal salts of sulfosuccinates and mixtures of two or more of said substances, more preferably wherein said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 81, polysorbate 85, dextran 12.000, dextran 70,000, fatty acid esters of glycerol and sorbitol as glycerol monostearate, sorbitan monostearate and sorbitan monooleate, polyoxamer 188 (Pluronic R F68), ethoxylated ethers, ethoxylated esters, ethoxylated triglycerides, ethoxylated phenols

and diphenols, metal salts of fatty acids and of fatty alcohol sulfates, more preferably the sodium salts of fatty acids and of fatty alcohol sulfates, even more preferably sodium stearate and sodium lauryl sulfate, and mixtures of two or more of said substances, even more preferably polysorbate 80, polysorbate 85, dextran 12,000 or dextran 70,000 and mixtures thereof and mixtures of the stabilizers/surfactants with other stabilizers/surfactants.

8. The use according to any of the claims 1 to 7, wherein said carrier and/or diluent is/are selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts and/or buffers and any other solution acceptable for administration to a mammal.

9. The use according to any of the claims 1 to 8, wherein the administration is an i. v. administration.

10. The use according to any of the claims 1 to 9, wherein said mammal is a human.

11. Nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the treatment of cancer in said mammal.

12. A process for the treatment of cancer, particularly of brain cancer, in mammals, said process comprising the step of administering to said mammals nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a

mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, in an amount effective for the treatment of cancer.

13. The process of claim 12, wherein the administration is an i.v. or i.p. administration.

14. The process according to claim 12 or claim 13, wherein the treatment is a treatment of brain cancer.

Declaration and Power of Attorney for Patent Application
Erklärung für Patentanmeldungen mit Vollmacht
German Language Declaration

Als nachstehend benannter Erfinder erkläre ich hiermit an Eides Statt:

As a below named inventor, I hereby declare that:

daß mein Wohnsitz, meine Postanschrift und meine Staatsangehörigkeit den im nachstehenden nach meinem Namen aufgeführten Angaben entsprechen, daß ich nach bestem Wissen der ursprüngliche, erste und alleinige Erfinder (falls nachstehend nur ein Name angegeben ist) oder ein ursprünglicher, erster und Miterfinder (falls nachstehend mehrere Namen aufgeführt sind) des Gegenstandes bin, für den dieser Antrag gestellt wird und für den ein Patent für die Erfindung mit folgendem Titel beantragt wird

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

deren Beschreibung:

- ☐ ist beigefügt
- ☐ wurde angemeldet am _____

unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertratgs über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT)

_____ und am

_____ abgeändert (falls zutreffend)

the specification of which

- ☐ is attached hereto
- X☐ was filed on JUNE 2, 1999

as United States Application Number or PCT International Application Number

PCT/EP99/03838 and was amended on

_____ (if applicable).

Ich bestätige hiermit, daß ich den Inhalt der oben angegebenen Patentanmeldung, einschließlich der Ansprüche, die eventuell durch einen oben erwähnten Zusatzantrag abgeändert wurde, durchgesehen und verstanden habe

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Ich erkenne meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfähigkeit in Einklang mit Titel 37, Code of Federal Regulations, § 1.56 von Belang sind.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56

German Language Declaration

Ich beanspruche hiermit ausländische Prioritätsvorteile gemäß Title 35, US-Code, § 119(a)-(d), bzw § 365(b) aller unten aufgeführten Auslandsanmeldungen für Patente oder Erfinderurkunden, oder § 365(a) aller PCT internationalen Anmeldungen, welche wenigstens ein Land ausser den Vereinigten Staaten von Amerika benennen, und habe nachstehend durch ankreuzen sämtliche Auslandsanmeldungen für Patente bzw. Erfinderurkunden oder PCT internationale Anmeldungen angegeben, deren Anmeldetag dem der Anmeldung, fur welche Priorität beansprucht wird, vorangeht

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s)
(Frühere auslandische Anmeldungen)

(Number) (Nummer)	(Country) (Land)	(Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung)	Priority claimed Priorität beansprucht ☐ Yes Ja	☐ No Nein
			☐ Yes Ja	☐ No Nein

Ich Beanspruche hiermit Prioritätsvorteile unter Title 35, US-Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below

(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)	(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)

Ich beanspruche hiermit die mir unter Title 35, US-Code, § 120 zustehenden Vorteile aller unten aufgeführten US-Patentanmeldungen bzw. § 365(c) aller PCT internationalen Anmeldungen, welche die Vereinigten Staaten von Amerika benennen, und erkenne, insofern der Gegenstand eines jeden fruheren Anspruchs dieser Patentanmeldung nicht in einer US-Patentanmeldung, bzw PCT internationalen Anmeldung in in einer gemaß dem ersten Absatz von Title 35, US-Code § 112 vorgeschriebenen Art und Weise offenbart wurde, meine Pflicht zur Offenbarung jeglicher Informationen an, die zur Prüfung der Patentfahigkeit in Einklang mit Title 37, Code of Federal Regulations, § 1 56 von Belang sind und die im Zeitraum zwischen dem Anmeldetag der fruheren Patentanmeldung und dem nationalen oder im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesen (PCT) gültigen internationalen Anmeldetags bekannt geworden sind.

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PCT/EP99/03838 (Application No.) (Aktenzeichen)	2 JUNE 1999 (Filing Date) (Anmeldetag)	(Status) (patented, pending, abandoned) (Status) (patentiert, schwebend, aufgegeben)
		(Status) (patented, pending, abandoned) (Status) (patentiert, schwebend, aufgegeben)

Ich erkläre hiermit, daß alle in der vorliegenden Erklärung von mir gemachten Angaben nach bestem Wissen und Gewissen der Wahrheit entsprechen, und ferner daß ich diese eidesstattliche Erklärung in Kenntnis dessen ablege, daß wissentlich und vorsätzlich falsche Angaben oder dergleichen gemaß § 1001, Title 18 des US-Code strafbar sind und mit Geldstrafe und/oder Gefängnis bestraft werden können und daß derartige wissentlich und vorsätzlich falsche Angaben die Rechtswirksamkeit der vorliegenden Patentanmeldung oder eines aufgrund deren erteilten Patentes gefahrden können

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

German Language Declaration

VERTRETUNGSVOLLMACHT: Als benannter Erfinder beauftrage ich hiermit den (die) nachstehend aufgefuhrten Patentanwalt (Patentanwälte) und/oder Vertreter mit der Verfolgung der vorliegenden Patentanmeldung sowie mit der Abwicklung aller damit verbundenen Angelegenheiten vor dem US-Patent- und Markenamt: *(Name(n) und Registrationsnummer(n) auflisten)*

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: *(list name and registration number)*

Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913, C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870, Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294, with full powers of substitution and revocation.

Postanschrift

Send Correspondence to:
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Vor- und Zuname des einzigen oder ersten Erfinders 100	Full name of sole or first inventor Bernhard A. SABEL
Unterschrift des Erfinders Datum	Inventor's signature ✓ Date ✓
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Staatsangehorigkeit	Citizenship Germany
Postanschrift	Post Office Address same as above
Vor- und Zuname des zweiten Miterfinders (falls zutreffend) 200	Full name of second joint inventor, if any Joerg KREUTER
Unterschrift des zweiten Erfinders Datum	Second inventor's signature ✓ Date ✓ 19.3.2001
Wohnsitz	Residence Georg-August-Zinn Strasse 13, D-61350 Bad Homburg, Germany DEX
Staatsangehorigkeit	Citizenship Germany
Postanschrift	Post Office Address same as above

(Im Falle-dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufugen.)

(Supply similar information and signature for third and subsequent joint inventors)

German Language Declaration

Vor- und Zuname des dritten Miterfinders (falls Zutreffend) 3rd	Full name of third joint inventor, if any Svetlana GELPERINA
Unterschrift des dritten Erfinders Datum	Third inventor's signature Date ✓Gelperina ✓2003.01
Wohnsitz	Residence Apartment No. 719 ul. Profsojuznaya, 113-3, Moscow, 117647, Russia RUX
Staatsangehörigkeit	Citizenship Russia
Postanschrift	Post Office Address same as above
Vor- und Zuname des vierten Miterfinders (falls Zutreffend)	Full name of fourth joint inventor, if any Ulrike SCHROEDER
Unterschrift des vierten Erfinders Datum	Fourth inventor's signature Date ✓ ✓
Wohnsitz	Residence Am Suelzehang 7, D-39171 Dodendorf, Germany
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Vor- und Zuname des fünften Miterfinders (falls Zutreffend)	Full name of fifth joint inventor, if any
Unterschrift des fünften Erfinders Datum	Fifth inventor's signature Date
Wohnsitz	Residence
Staatsangehorigkeit	Citizenship
Postanschrift	Post Office Address
Vor- und Zuname des sechsten Miterfinders (falls Zutreffend)	Full name of sixth joint inventor, if any
Unterschrift des sechsten Erfinders Datum	Sixth inventor's signature Date
Wohnsitz	Residence
Staatsangehörigkeit	Citizenship
Postanschrift	Post Office Address

(Im Falle dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufugen.)

(Supply similar information and signature for third and subsequent joint inventors.)

German Language Declaration

Vor- und Zuname des dritten Miterfinders (falls Zutreffend)	Full name of third joint inventor, if any Svetlana GELPERINA
Unterschrift des dritten Erfinders Datum	Third inventor's signature Date ✓ ✓
Wohnsitz	Residence Apartment No. 719 ul. Profsojuznaya, 113-3, Moscow, 117647, Russia
Staatsangehörigkeit	Citizenship Russia
Postanschrift	Post Office Address same as above
Vor- und Zuname des vierten Miterfinders (falls Zutreffend) 400	Full name of fourth joint inventor, if any Ulrike ~~SCHROEDER~~
Unterschrift des vierten Erfinders Datum	Fourth inventor's signature Date ✓ U. Schröder ✓ 21.3.01
Wohnsitz	Residence Am Suelzehang 7, D-39171 Dodendorf, Germany DEX
Staatsangehörigkeit	Citizenship Germany
Postanschrift	Post Office Address same as above
Vor- und Zuname des fünften Miterfinders (falls Zutreffend)	Full name of fifth joint inventor, if any
Unterschrift des fünften Erfinders Datum	Fifth inventor's signature Date
Wohnsitz	Residence
Staatsangehorigkeit	Citizenship
Postanschrift	Post Office Address
Vor- und Zuname des sechsten Miterfinders (falls Zutreffend)	Full name of sixth joint inventor, if any
Unterschrift des sechsten Erfinders Datum	Sixth inventor's signature Date
Wohnsitz	Residence
Staatsangehorigkeit	Citizenship
Postanschrift	Post Office Address

(Im Falle-dritter und weiterer Miterfinder sind die entsprechenden Informationen und Unterschriften hinzuzufugen)

(Supply similar information and signature for third and subsequent joint inventors.)

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

the specification of which

☐ is attached hereto.

☒ was filed on 02 FEBRUARY 2001 as

Application Serial No. 09/774,181

and amended on _____.

☒ was filed as PCT international application

Number PCT/EP99/03838

on 02 JUNE 1999,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

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✓ 21. März 2007
Date

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Signature of Inventor

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Date